Staff Writer
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Alcoholic Pancreatitis Patients with Continued Alcohol Intake May Finally Have Therapeutic Options

Many alcoholic pancreatitis patients continued drinking during COVID-19. University of Miami Miller School of Medicine researchers study the effects of continued alcohol intake and seek better treatment for alcohol-associated pancreatic disease.

Dr. Nagaraj Nagathihalli, lead author, and Dr. Siddharth Mehra, first author

Researchers at the Miller School are looking for solutions to the continued effects of alcohol use, its harmful impact, and treatment. Understanding the mechanisms of alcohol abuse has gained importance, especially after the COVID-19 pandemic. Higher alcohol consumption led to an increased burden of pancreatic diseases in society.

In a study titled “Urolithin A attenuates severity of chronic pancreatitis associated with continued alcohol intake by inhibiting PI3K/AKT/mTOR signaling,” published in the *American Journal of Physiology – Gastrointestinal and Liver Physiology*, researchers examine the short- and long-term consequences of this increased alcohol effect on pancreatic diseases and work together on innovative approaches to better understand how to

treat pancreatitis patients with continued alcohol intake.

Pancreatitis is inflammation of the pancreas often associated with long-term alcohol consumption, a potential risk factor for the induction of acute pancreatitis. Recurrent attacks of acute pancreatitis results in chronic pancreatitis. Each year, about 275,000 hospital stays for acute pancreatitis and 86,000 hospital stays for chronic pancreatitis occur across the U.S., according to the statistics released by the National Institute of Diabetes and Digestive and Kidney Diseases.

Acute pancreatitis appears suddenly and can typically be resolved in days with treatment in most patients. However, acute pancreatitis can also cause severe life-threatening conditions in some cases. Recurrent episodes of acute pancreatitis instigate irreversible damage to the pancreas, causing weight loss, pain, diabetes, and even pancreatic cancer.

Alcohol Use Spiked during COVID-19

Total alcohol sales almost tripled in the U.S. during the COVID-19 pandemic, subsequently increasing the number of patients diagnosed with alcohol-associated pancreatitis. Excessive alcohol consumption is associated with 40-70% of pancreatitis cases. Without moderation, alcohol use harshly impacts both the liver and pancreas, causing fat accumulation and inflammation, disrupting normal function.

With repeated episodes of binge drinking (four to five drinks in two hours), the pancreas eventually builds up scar tissues with persistent inflammation, weakening its endocrine and exocrine functions needed to digest food and regulate blood sugar levels. This chronic insult to the organ can cause

excruciating pain, malnutrition, diabetes, and death.

Dr. Nagathihalli and Dr. Mehra in the pancreas laboratory at the University of Miami Miller School of Medicine

“We are developing novel models to study and to prevent inflammation or reverse the pancreatic damage caused due to excess alcohol intake,” said lead author Nagaraj Nagathihalli, Ph.D., associate professor of surgery in the DeWitt Daughtry Family Department of Surgery, Division of Surgical Oncology.

Continued Alcohol Use Perpetuates Pancreatic Injury in Mice Models

Accumulating scientific evidence suggests that continued alcohol consumption with established alcoholic pancreatitis instigates irreversible pancreatic damage due to recurrent episodes of acute pancreatitis by fostering a continuous fibro-inflammatory microenvironment within the pancreas.

“The molecular mechanisms involved in the pathophysiology of alcoholic pancreatitis with continuous alcohol intake remains ambiguous; treatment options and preventative care strategies are restricted due to limited experimental animal models that successfully recapitulate human pancreatitis arising from prolonged or continued alcohol use after established pancreatic injury,” said Dr. Nagathihalli.

“In this study, using an established alcoholic pancreatitis mice model, we have addressed two of the major unanswered

questions with regards to the pathogenesis of pancreatitis. We've characterized the pancreas-specific signaling pathways in this process and determined if utilizing novel therapeutic agents can attenuate the severity of alcoholic pancreatitis progression, despite continued alcohol triggers" said first author of the study Siddharth Mehra, Ph.D., a postdoctoral fellow in the Miller School's Department of Surgery.

Preventing Alcohol-associated Chronic Pancreatitis May Benefit Patients with Difficulty in Alcohol Abstinence

The microbiome has been implicated in gastrointestinal inflammation as a critical mediator of overall gut health. Urolithin A is a natural compound synthesized by gut bacteria from ingested ellagitannins, a class of hydrolyzable tannins found mainly in pomegranate, berries, and nuts. Previous work from the group has shown that Urolithin A is a potent anti-inflammatory agent in several pre-clinical disease models and exhibits anti-tumor activity in gastrointestinal cancers.

"Our studies have demonstrated that Urolithin A is well tolerated and does not elicit any adverse toxic effects at clinically relevant doses in mice. However, despite the promising effect of Urolithin A in several malignancies and inflammatory disorders, the benefit of this microbial metabolite in the prevention of pancreatitis had not been investigated," says Dr. Nagathihalli. The FDA recognizes Urolithin A as a "safe dietary supplement."

"In animal experiments, we have shown that Urolithin A can help improve the effectiveness of treating alcoholic pancreatitis despite continued alcohol intake," said Dr. Mehra.

Co-authors of the study include Dr. Chanjuan Shi of Duke University; Dr. Michael VanSaun of the University of Kansas; Dr. Venkatakrishna Jala of the University of Louisville; and Supriya Srinivasan, Ph.D., Samara Singh, Zhiqun Zhou, M.D., Vanessa Garrido, Ph.D., Iago Castro Silva, M.D., Tulasigeri Totiger, Ph.D., Austin Dosch, M.D., Xizi Dai, Ph.D., Rajinder Dawra, Ph.D., Jashodeep Datta, M.D., and Nipun Merchant, M.D., of the Miller School of Medicine.

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